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Histone deacetylase as a therapeutic target

Oliver H. Krämer, Martin Göttlicher and Thorsten Heinzel

The maintenance of health depends on the coordinated and tightly regulated expression of genetic information. Certain forms of leukemia have become paradigms for the pathogenic role of aberrant repression of differentiation genes. In these acute leukemias, fusion proteins generated by chromosomal translocations no longer function as transcriptional activators, but instead repress target genes by recruiting histone deacetylases (HDACs). The potential benefit of HDAC inhibition has been established by the use of enzyme inhibitors *in vitro* and in a single reported case of experimental therapy. Because recently identified HDAC inhibitors appear to overcome many drawbacks of early inhibitory compounds in clinical use, the stage is set to test the therapeutic value of HDAC inhibition in leukemias and in other diseases, including solid tumors and aberrant hormonal signaling. This review summarizes the range of diseases expected to respond to HDAC inhibition.

Local remodeling of chromatin and dynamic changes in nucleosomal packaging of DNA are key steps in the regulation of gene expression and consequently affect proper cell function, differentiation and proliferation. One of the most important mechanisms determining the activity of target genes is the post-translational modification of the N-terminal tails of

core histones by acetylation and subsequent changes in chromatin structure^{1–3}. Acetylation of Lys residues, predominantly in histones H3 and H4, is mediated by enzymes with HAT (see Glossary) activity. Conversely, acetyl groups are removed from ε-N-acetyl-lysine by HDACs. Both HAT and HDAC activities can be recruited to target genes in complexes with sequence-specific transcription factors and their cofactors. Nuclear receptors of the steroid/retinoid receptor superfamily, such as RAR or thyroid hormone receptor, are prototypical examples of transcription factors that depend on activation by an appropriate ligand for the recruitment of HAT- and HDAC-associated cofactors. In the absence of ligand, these nuclear receptors interact with corepressors, such as N-COR and SMRT. The corepressors form large protein complexes containing HDACs and thereby inhibit transcription⁴. Upon ligand binding, the corepressor complex dissociates and is replaced by coactivator proteins, such as SRC-1 and CBP, which exist in

Glossary

AML: acute myeloid leukemia	mSin3: mammalian homolog of yeast Sin3 (SWI-independent)
APL: acute promyelocytic leukemia	MTA: metastasis-associated protein
bak: bcl2-antagonist/killer1	N-CoR: nuclear receptor corepressor
CBP: CREB-binding protein	NMU: N-methyl-N-nitrosourea
CBHA: M-carboxy-cinnamic acid bishydroxamide	NY-ESO: autoimmunogenic cancer/testis antigen
CDKN: cyclin-dependent kinase inhibitor	PLZF: promyelocytic zinc finger protein
CHAP: cyclic hydroxamic acid-containing peptide	PML: promyelocytic leukemia protein
CRAB: cellular retinoid acid-binding protein	RA: retinoic acid
DAC: 5-aza-2'-deoxycytidine	RAR: retinoic acid receptor
ETO: eight-twenty-one translocation	Rpd3: histone deacetylase, originally defined as a mutation causing reduced potassium dependency in yeast
GATA: GATA-binding protein	RTH: resistance to thyroid hormone
HAT: histone acetyltransferase	SAHA: suberoylanilide hydroxamic acid
HDAC: histone deacetylase	Sir: silencing information regulator
HIF: hypoxia-inducible factor	SMRT: silencing mediator of retinoic acid and thyroid hormone receptor
ID1-3: inhibitor of differentiation 1-3	SRC: steroid receptor coactivator
Mad: max (myc-associated factor X) dimerization protein	T₃: triiodothyronine
MAGE: melanoma-associated antigen gene	TIMP: tissue inhibitor of metalloproteinase
Mi-2: ATP-dependent DNA-helicase, major antigenic protein of the dermatomyositis-specific Mi-2 autoantigen	TSA: trichostatin A
MLH: MutL heterodimer	VEGF: vascular endothelial growth factor

multiprotein complexes harboring HAT activity. The ligand-induced switch of nuclear receptors from repression to activation thus reflects the exchange of corepressor and coactivator complexes with antagonistic enzymatic activities⁵. Intriguingly, many other transcription factors, such as Mad-1, BCL-6 and ETO (Refs 4,6-9) have also been shown to assemble HDAC-dependent transcriptional repressor complexes, suggesting that this is a common mechanism of gene regulation.

Histone deacetylases

Mammalian HDACs can be divided into three subclasses^{10,11}. Class I enzymes are homologous to the yeast rpd3 protein and include the mammalian HDAC1, HDAC2, HDAC3 and HDAC8 enzymes, whose molecular masses range from 42-55 kDa. Class II HDACs (HDAC4, HDAC5, HDAC6 and HDAC7) are larger proteins (~120-130 kDa) that are related to the yeast Hda1 protein. Recently, a third class of HDACs, with homology to the yeast sir2 protein and several putative mammalian members, has been identified¹². As of now, it is still unclear to what extent these HDACs exert isoenzyme-specific or redundant functions. Further studies, including gene-deletion analysis, are therefore required to elucidate the biological roles of each of these enzymes.

HDACs bind to many different proteins and usually exist in large complexes within the cell. Many of the associated proteins seem to be involved in targeting HDACs to their substrates or to transcriptional repressors. For example, the Rb-associated proteins RbAP46 and RbAP48 are usually considered as integral to the HDAC enzyme complex, which is responsible for the recognition of nucleosomal substrates^{13,14}. By contrast, the corepressors N-CoR, SMRT and mSin3 are bridging factors that are required for the recruitment of HDACs to transcription factors¹⁵. HDACs are also

components of the nucleosome remodeling and deacetylase complex, which also contains RbAP46 and RbAP48, Mi-2 and MTA2 (Ref. 16). Given the large number of HDAC isoenzymes and interacting proteins, it is conceivable that complex composition could modulate substrate specificity and might even target HDACs to non-histone proteins.

Aberrant repression in disease

Inappropriate repression of genes required for cell differentiation has been linked to several forms of cancer and, in particular, to acute leukemia. In acute APL patients, RAR fusion proteins, resulting from chromosomal translocations, involve either the PML or the PLZF (Ref. 17). Both fusion proteins can interact with components of the corepressor complex. The addition of high doses of all-*trans* retinoic acid, however, dismisses the corepressor complex only from PML-RAR, but not from PLZF-RAR (Refs 18-21). These findings provide an explanation why PML-RAR-APL patients usually achieve complete remission upon retinoic acid treatment, whereas PLZF-RAR-APL patients respond very poorly to this therapy. The hypothesis that corepressor-mediated aberrant repression might cause pathogenesis in APL patients is supported by the finding that inhibitors of corepressor-associated HDAC activity are capable of overcoming the differentiation block in cells containing the PLZF-RAR fusion protein.

In a frequent form of AML, the translocation t(8;21) results in the AML1-ETO fusion protein, in which the transactivation domain of transcription factor AML1 is replaced by the almost complete ETO protein. The translocation partner ETO has been reported to interact with N-CoR, SMRT, mSin3 and HDACs (Refs 7-9,22). Thus, the fusion protein recruits corepressor complexes containing HDAC activity instead of recruiting coactivators. Recent reports indicate that the oncogenic potential and

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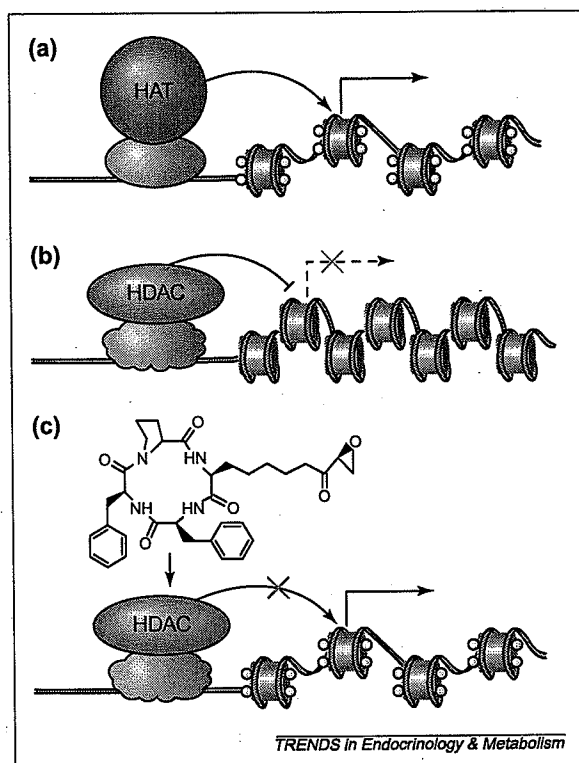


Fig. 1. Relief of aberrant repression by HDAC inhibitors. (a) In the healthy organism an intact transcription factor (represented by a blue oval) associated with a coactivator complex (green sphere) harboring histone acetyltransferase activity (HAT) binds to specific promoter sequences. Histone acetylation (yellow spheres) leads to a relaxed chromatin structure, enabling transcription of target genes required for cell differentiation (represented by an arrow). (b) The properties of the transcription factor are changed by mutation so that it can no longer activate transcription but instead becomes a constitutive repressor (distorted blue shape) binding corepressor complexes (red oval) containing histone deacetylases (HDAC). Transcriptional repression of target genes, mediated by histone deacetylation and subsequent condensation of chromatin, ultimately contributes to cell transformation. (c) HDAC inhibitors such as trapoxin block HDAC enzymatic activity and thereby induce the accumulation of hyperacetylated histones. The resulting relaxed chromatin structure permits expression of target genes at levels similar to those seen in the wild-type situation. This process can contribute to the arrest of tumor-cell growth and the re-differentiation of transformed cells.

transcriptional repressor activity of the translocation product AML1-ETO requires oligomerization²³. In non-Hodgkin's lymphoma, translocations and point mutations frequently lead to overexpression of the BCL-6 oncogene product, which has been implicated in the control of B-cell proliferation. Because BCL-6 is a transcription factor that interacts with the corepressors N-CoR and SMRT, aberrant repression, as occurs in acute leukemias, could also be involved in the pathogenesis of non-Hodgkin's lymphoma⁶.

Mutations in a nuclear hormone receptor have also been implicated as causal agents in RTH, an endocrine human genetic disease characterized by a disruption in both negative-feedback regulation and in positive regulation by T_3 . Diverse dominant negative mutations in the thyroid hormone receptor β gene, causing constitutive binding of corepressors and associated HDACs, are the molecular basis of RTH (Refs 24,25).

Because pathogenesis in acute leukemia and non-Hodgkin's lymphoma is associated with the aberrant repression of genes required for cell differentiation, it is plausible that this mechanism could also be relevant to many additional types of cancer, including solid tumors. Currently, the molecular basis of many neoplasias is still largely unexplored. Owing to the link between transcriptional repression and the recruitment of HDACs, inhibitors of this enzymatic activity are expected to reverse repression and to induce re-expression of differentiation-inducing genes (Fig. 1). Therefore, HDAC inhibitors are potentially promising candidate drugs for differentiation therapy of cancer and the treatment of certain endocrine diseases.

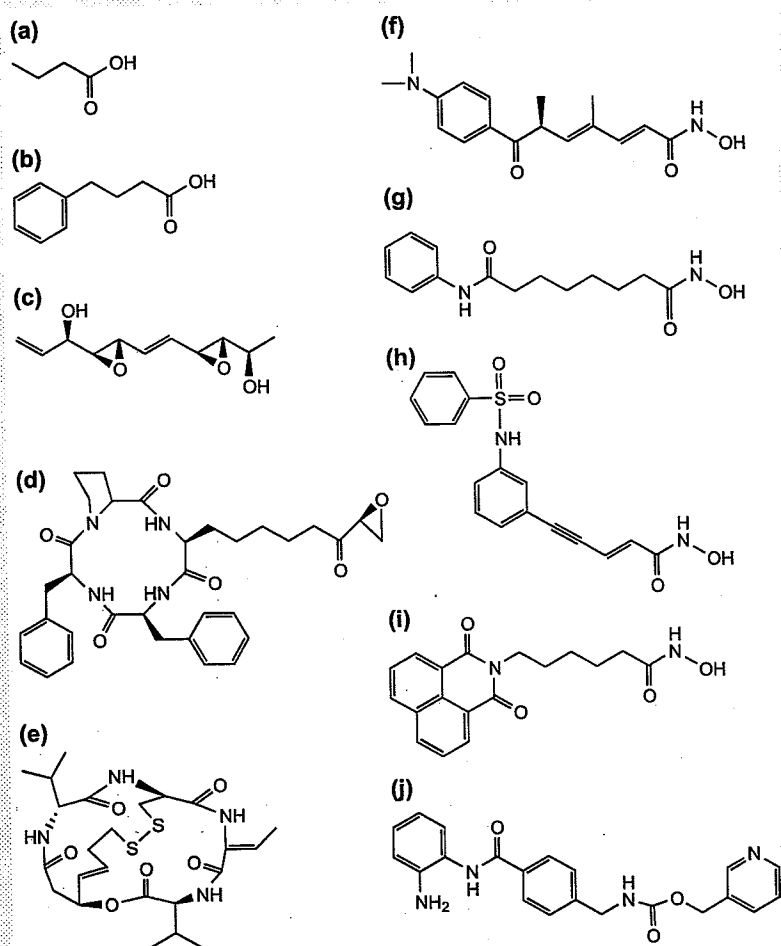
HDAC inhibitors

Compounds shown to inhibit the activity of HDACs fall into six structurally diverse classes (Box 1). Butyrate was the first HDAC inhibitor to be identified²⁶ and the related compound phenylbutyrate has been successfully employed in experimental cancer therapy²⁷. However, butyrates are far less potent than other HDAC inhibitors (Box 1) and only at millimolar concentrations do they inhibit HDACs *in vivo* by a noncompetitive mechanism that is not fully understood²⁸. Furthermore, butyrate is not specific for HDACs but, in addition to DNA methylation, also affects metabolism and other enzyme systems, such as those mediating phosphorylation and methylation of proteins²⁸. Moreover, in spite of a low toxicity profile, butyrates are of limited clinical benefit for the treatment of certain cancers because they have a short serum-half-life in humans²⁹⁻³¹.

Other HDAC inhibitors are more specific and are active at much lower concentrations (Box 1; Ref. 32). Trapoxin and depudecin irreversibly bind to and inactivate HDAC enzymes^{33,34}. Hydroxamic acids such as TSA or SAHA and other HDAC inhibitors reversibly inhibit HDAC enzymes. X-ray crystallographic studies of an archaeobacterial HDAC homolog have revealed the structure of the catalytic core of HDACs and the mode by which hydroxamic acid HDAC inhibitors (TSA, SAHA) bind to the pocket of the catalytic site³⁵. This structural analysis has been complemented by extensive structure-activity studies in a series of hydroxamic acid-based hybrid polar compounds related to SAHA and TSA (Ref. 36). Competition with substrates for the catalytic center has also been proposed as the mechanism by which other compounds inhibit HDACs.

These findings should be of great benefit for the development of improved specific HDAC inhibitors with low toxicity and reduced side effects. This appears to be very important, because many HDAC inhibitors either exhibit considerable toxicity or have poor bioavailability and thus are of limited therapeutic use. The toxicity of those substances initially isolated from microorganisms³⁷ could be a

Box 1. Chemical structures of selected HDAC inhibitors



TRENDS in Endocrinology & Metabolism

Inhibitor	MM (Da)	Structural class ^a	Effective inhibitory concentration range ^b	Refs
a Butyric acid	88.1	SCFAs and derivatives	mM	26
b Phenylbutyrate	165.2	SCFAs and derivatives	mM	79
c Depudecin	210.2	Epoxides	μM; irreversible binding	34
d Trapoxin	589.3	CTs containing an AOE moiety	nM; irreversible binding	33
e Depsipeptide	541.7	CTs lacking an AOE moiety	μM	52
f TSA	302.4	HAs	μM	41
g SAHA	264.3	HAs	μM	80
h Scriptaid	326.4	HAs	μM	54
i Oxamflatin	342.4	HAs	μM	40
j MS-27-275	376.4	Benzamides	μM	44

^aAbbreviations: see Glossary; AOE, 2-amino-8-oxo-9,10-epoxy-decanoil; CT, cyclic tetrapeptide; HA, hydroxamic acid; MM, molecular mass; SCFA, short chain fatty acid.
^bSee Refs 36,54.

Table 1. Cell lines sensitive to growth inhibition by HDAC inhibitors

Origin of cell line	Refs
Bladder	50
Bone	51
Breast	52-54
Cervix	40,50
Colon	40,44,53,55-58
CNS	55,59
Esophagus	48
Gastric	44
Lung	40,44,48
Leukemia	20,40,44,47,60
Liver	30
Oral	44
Ovary	44,53
Pancreas	30,44,54
Prostate	31,43
Retinoblastoma	30
Skin	42
Thorax	49

seem to inhibit certain HDACs preferentially, as has been shown for trapoxin and the related CHAP1 (Ref. 38). Further structural data, in addition to data on specific functions of individual mammalian HDACs and different HDAC-containing complexes, are clearly needed.

In vitro model systems for HDAC inhibitors

There is ample evidence, both *in vitro* and *in vivo*, that HDAC inhibitors block the enzymatic activity of deacetylases and induce hyperacetylation of histones³⁶. Furthermore, a plethora of cultured tumor cells has been tested for susceptibility to HDAC inhibition (Table 1). Upon treatment with HDAC inhibitors, these cells show signs of apoptosis, growth arrest, differentiation and altered gene expression. However, in many cases it is unclear whether these effects resulted from an altered gene-expression profile or were caused by toxic effects inherent to the substances employed. After treatment with TSA or SAHA, only a small subset of genes (around 2%) was found to have significantly altered levels of expression, although effects on bulk histone acetylation were observed^{36,39}. Because these studies were performed under conditions of ongoing protein synthesis, even fewer genes would be expected to be affected directly. This indicates that merely a subpopulation of genes is controlled by histone deacetylation alone, and argues for specific effects exerted by HDAC inhibitors. The responsiveness of only a relatively small subset of genes might also be the reason why HDAC inhibitors appear to affect tumor cells preferentially, rather than being toxic to the whole organism. Moreover, normal cells were found to be less sensitive to effects caused by

consequence of evolutionary selection, because their likely biological role is to kill competitors and enemies efficiently, possibly by multiple mechanisms in addition to HDAC inhibition. A further parameter for the development of novel HDAC inhibitors is suggested by the finding that some HDAC inhibitors

Table 2. Genes that are affected by HDAC inhibitors^a

Upregulated genes	Downregulated genes	Substance	Refs
p21 ^{waf/cip1} , GATA-2, hsp86, ID1-3	bcl-X _L , CRAB2, TFIID/TAF _{II} 31	TSA	61
p21 ^{waf/cip1} , gelsolin, cyclin E	cyclin A, cyclin D	Oxamflatin	40
p21 ^{waf/cip1}	c-myc, c-myb, B-myb	SAHA	60
p21 ^{waf/cip1} , p27, TGF-β1		TSA	62
p21 ^{waf/cip1} , gelsolin		MS-27-275	44
p21 ^{waf/cip1} , MLH1, TIMP3, CDKN2A, CDKN2B		TSA + DAC	63
p21 ^{waf/cip1}		Butyrate	53
p21 ^{waf/cip1} , cyclin E	cyclin A	TSA	56
	plasminogen activator urokinase, cyclin D1/prad1	Butyrate	64
HDAC1	p57 ^{kip2}	TSA	65
RAR-β		Phenylbutyrate + RA	31
MHC-1, MHC-2, CD40		TSA, butyrate	55
IL-8, urokinase receptor		Butyrate	58
IFN-γ	CD154, IL-10	TSA	66
TGF-β receptor II		MS-27-275	67
IGFBP-3		TSA	68
CD95, CD95L		CBHA	59
MAGE-3		Depsipeptide + DAC	48
NY-ESO-1		Depsipeptide + DAC	49
p53, von Hippel-Lindau	HIF-1α, VEGF	TSA	46
bak	bcl-2	Butyrate	69
p107, dihydrofolate reductase		TSA	70

^aSee Glossary for abbreviations.

inhibition of HDACs (Ref. 40), reflecting different modes of gene activation in these cells compared with their transformed counterparts. Nevertheless, particularly sensitive tissues might exist under certain physiological conditions or during specific phases of embryonic development. To understand the apparent preferential sensitivity of tumor cells, a crucial subset of genes, specifically mediating the effects of HDAC inhibitors on tumor-cell proliferation or survival, has to be identified.

In the variety of cell lines studied, synthesis of p21^{WAF1}, a cyclin-dependent kinase inhibitor, has been found to be induced most consistently (Table 2). This could explain the G₁ arrest and G₂/M block that

is frequently observed in cells treated with HDAC inhibitors. Other genes exhibiting altered expression patterns are mainly factors regulating apoptosis and the cell cycle, molecules with immunological functions, and factors relevant to tumor development. Thus, changes in cell-cycle regulation and cell survival, in addition to enhanced immune surveillance, might contribute to the successful treatment with HDAC inhibitors seen *in vivo* (Table 2). Stringent causal links between altered gene expression and observed effects on proliferation or cell survival have, however, not been established in many experimental systems employed so far.

Although cell lines clearly exist that do not respond to the treatment with HDAC inhibitors^{41,42}, the range of tumor cells affected presents a promising perspective for anti-tumor activity in many different forms of cancer. Predictive tools to identify responsive tumors would be a valuable basis for deciding the treatment of individual patients with HDAC inhibitors. Identifying the derepressed target genes that are essential for the response of tumor cells to HDAC inhibition would aid in building these tools.

***In vivo* model systems for HDAC inhibitors**

Several experiments employing rodent models for cancer have shown that HDAC inhibitors significantly reduce the growth of tumors and metastases *in vivo* (Table 3). Notably, several of the compounds tested lacked considerable side effects at doses where tumor growth was inhibited markedly^{43,44}. This demonstrates the advantages of these compounds over phenylbutyrate and TSA (Refs 32,45). However, compared to *in vitro* cell-culture experiments, significantly higher doses of inhibitor had to be employed to affect tumor growth *in vivo*^{40,43,44,46}. The high doses required might be a result of poor bioavailability or rapid degradation of the compounds tested. Proof of the dose required for efficient HDAC inhibition by any compound considered for use *in vivo* is certainly needed. Detection of bulk histone acetylation in organs or leukocyte extracts could serve that purpose. Taken together, the effects of HDAC inhibitors in animal model systems clearly provide evidence that they preferentially affect tumor cells, rather than causing general toxicity to individual organs or to the whole organism. Thus, clinical studies for a variety of cancer forms appear to be well justified.

Clinical use of HDAC inhibitors

The clinical benefits of HDAC inhibition and their implications for re-differentiation therapy are currently being investigated in several locations. A PML-RAR patient who had experienced multiple relapses after treatment with retinoic acid and chemotherapy has been treated with the HDAC inhibitor phenylbutyrate, resulting in complete remission of the leukemia²⁷. The result of this initial

Table 3. *In vivo* experiments with HDAC inhibitors^a

Tumor	HDAC inhibitor	Refs
Colon	Butyrate	53,71,72
Colon, gastric, leukemia, lung, ovary, oral, pancreas	MS-27-275	44
Lung	TSA	46
Melanoma	Oxamflatin, hydroxamates	32,40
Prostate	SAHA, phenylbutyrate	31,43
MMU-induced mammary tumor	SAHA	73

^aSee Glossary for abbreviations.

Table 4. Clinical studies with HDAC inhibitors^a

HDAC inhibitor	Status	Disease	Refs
Butyric acid derivatives	compassionate use	APL	27
	compassionate use	AML	74
	pilot study	t(8;21) AML	NHLBI
	Phase I		31
	Phase I/II	malignant glioma	NABTT
	nd	nd	29,75,76
SAHA, pyroxamide	Phase I		36
Depsipeptide	nd	nd	38
(FR901228, FK228)	Phase I		ASCO study,77,78
	Phase II	T-cell lymphoma	NCI clinical trial
MS-27-275	Phase I		38,78

^aAbbreviations: see Glossary; ASCO, American Society of Clinical Oncology; NABTT, New Approaches to Brain Tumor Therapy; NCI, National Cancer Institute; nd, not determined; NHLBI, National Heart, Lung and Blood Institute.

study suggests that high doses of HDAC inhibitors do not need to be permanently sustained to achieve a clinical response. Phase I clinical trials in healthy volunteers for derivatives of butyric acid, SAHA, MS-27-275 and depsipeptide are currently under way (Table 4). Subsequent Phase II studies in cancer patients will test the effectiveness of HDAC inhibitors in therapy. Moreover, we also expect new and better compounds to enter the clinics in the near future.

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Perspectives

Currently available HDAC inhibitors have to be considered first-generation drugs. They will provide

further evidence for the feasibility of differentiation therapy of cancer and the treatment of abnormal hormonal signaling based on the reversal of transcriptional repression. The next step should be to identify additional responsive forms of cancer and to generate diagnostic tools. Further drug development will probably provide more selective non-toxic HDAC inhibitors. Specificity for individual HDAC isoenzymes could be another highly desirable goal once their biological roles have been firmly established.

Reversal of transcriptional repression by HDAC inhibition addresses a novel molecular target. Thus, combinations with established therapies can be expected to increase therapeutic efficiency. Combinations of HDAC inhibitors with retinoic acid have been shown to affect overlapping signaling pathways and to cause synergistic anti-tumor effects by potentiating and/or restoring retinoid-induced differentiation of transformed cells from APL patients⁴⁷. This finding suggests that a combination therapy could help to extend the therapeutic range of HDAC inhibitors to other tumors for which differentiation-inducing agents are available. Furthermore, the combination of established cytotoxic principles with HDAC inhibition would be expected to show additive or synergistic effects^{48,49}. The first generation of HDAC inhibitors provides the tools to put the therapeutic value of these compounds to the test in a variety of cancers and in combination with established therapeutic concepts.

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SPECIAL ARTICLE

RECOMMENDATIONS FOR THE MEDICAL MANAGEMENT OF OSTEOARTHRITIS OF THE HIP AND KNEE

2000 Update

AMERICAN COLLEGE OF RHEUMATOLOGY SUBCOMMITTEE ON OSTEOARTHRITIS GUIDELINES

Osteoarthritis (OA) is the most common form of arthritis in the United States (1). Patients with OA have pain that typically worsens with weight bearing and activity and improves with rest, as well as morning stiffness and gelling of the involved joint after periods of inactivity. On physical examination, they often have tenderness on palpation, bony enlargement, crepitus on motion, and/or limitation of joint motion. Unlike the

case with rheumatoid arthritis (RA) and other inflammatory arthritides, inflammation, if present, is usually mild and localized to the affected joint. Although the causes of OA are not completely understood, biomechanical stresses affecting the articular cartilage and subchondral bone, biochemical changes in the articular cartilage and synovial membrane, and genetic factors are all important in its pathogenesis (2–4).

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Although there is no known cure for OA, treatment designed for the individual patient can reduce pain, maintain and/or improve joint mobility, and limit functional impairment. In 1995, the American College of Rheumatology (ACR) published recommendations for the medical management of OA of the hip and knee (5,6). Those guidelines outlined the use of nonpharmacologic modalities, including patient education and physical and occupational therapy—the foundation of treatment of individuals with OA—as well as the use of pharmacologic agents. Specific recommendations for surgical management of OA, however, were not included. Since that time, several systematic reviews of drug therapy for OA have been published (7–11), and many clinical trials have been conducted which have resulted in the approval, or pending review, by the Food and Drug Administration (FDA) of new devices and drug treatments for OA.

In 1998, the ACR established an ad hoc subcommittee, comprising several of the American authors of the 1995 recommendations, to review interim developments in the field and update the recommendations. As in the original review, the subcommittee followed the

principles of evidence-based medicine as used in the process of making clinical decisions (12). As stated by Guyatt, "Physicians practicing [evidence-based medicine] will search for the highest evidence available, integrate this evidence with their clinical experience and judgment, and acknowledge the value judgments implicit in moving from evidence to action" (12).

The strongest weight was given to data from systematic reviews, meta-analyses, and published findings of randomized controlled trials; data from randomized controlled trials presented as abstracts at scientific meetings were also considered. Where such data were not available, however, the subcommittee followed the approach taken by the Agency for Health Care Policy and Research, as outlined in the ACR document "Guidelines for the Development of Practice Guidelines," which combines a detailed, evidence-based approach with a process that accommodates expert opinion. This was utilized particularly in reviewing the recommendations for nonpharmacologic modalities, especially the use of assistive devices, bracing, and footwear. Finally, recently published data on OA patients' preferences regarding treatment with analgesics and nonsteroidal antiinflammatory drugs (NSAIDs) were also reviewed (13,14).

The goals of the contemporary management of the patient with OA continue to include control of pain and improvement in function and health-related quality of life, with avoidance, if possible, of toxic effects of therapy. The recommended approach to the medical management of hip or knee OA includes nonpharmacologic modalities and drug therapy. The Subcommittee on OA Guidelines emphasizes that these recommendations are not fixed, rigid mandates, and recognizes that the final decision concerning the therapeutic regimen for an individual patient rests with the treating physician.

Nonpharmacologic modalities

The components of nonpharmacologic therapy are outlined in Table 1. Patient education and, where appropriate, education of the patient's family, friends, or other caregivers are integral parts of the treatment plan for patients with OA. Patients should be encouraged to participate in self-management programs, such as the Arthritis Foundation Self-Management Program. Individuals who participate in these programs report decreases in joint pain and frequency of arthritis-related physician visits, increases in physical activity, and overall improvement in quality of life (15). Additional educational materials, including videos, pamphlets, and news-

Table 1. Nonpharmacologic therapy for patients with osteoarthritis

Patient education
Self-management programs (e.g., Arthritis Foundation Self-Management Program)
Personalized social support through telephone contact
Weight loss (if overweight)
Aerobic exercise programs
Physical therapy
Range-of-motion exercises
Muscle-strengthening exercises
Assistive devices for ambulation
Patellar taping
Appropriate footwear
Lateral-wedged insoles (for genu varum)
Bracing
Occupational therapy
Joint protection and energy conservation
Assistive devices for activities of daily living

letters, are available from the Arthritis Foundation and other national voluntary health organizations. Another cost-effective nonpharmacologic approach for patients with OA is provision of personalized social support, either directly or by periodic telephone contact. Studies of the results of monthly telephone calls by trained nonmedical personnel to discuss such issues as joint pain, medications and treatment compliance, drug toxicities, date of next scheduled visit, and barriers to keeping clinic appointments showed moderate-to-large degrees of improvement in pain and functional status without a significant increase in costs (16). These studies underscore the concept that improved communication and education are important factors in decreasing pain and improving function in patients with OA.

Individuals with OA of the lower extremity may have limitations that impair their ability to perform activities of daily living (ADLs), such as walking, bathing, dressing, use of the toilet, and performing household chores. Physical therapy and occupational therapy play central roles in the management of patients with functional limitations. The physical therapist assesses muscle strength, joint stability, and mobility; recommends the use of modalities such as heat (especially useful just prior to exercise); instructs patients in an exercise program to maintain or improve joint range of motion and periarticular muscle strength; and provides assistive devices, such as canes, crutches, or walkers, to improve ambulation. Similarly, the occupational therapist can be instrumental in directing the patient in proper joint protection and energy conservation, use of splints and other assistive devices, and improving joint function. In addition, the input of a vocational guidance

counselor may be important to patients who are still actively employed.

Quadriceps weakness is common among patients with knee OA, in whom it had been believed to be a manifestation of disuse atrophy, which develops because of unloading of the painful extremity. Recent studies, however, have indicated that quadriceps weakness may be present in persons with radiographic changes of OA who have no history of knee pain, and in whom lower extremity muscle mass is increased, rather than decreased (17); and that quadriceps weakness may be a risk factor for the development of knee OA, presumably by decreasing stability of the knee joint and reducing the shock-attenuating capacity of the muscle (18). These data have recently been reviewed by Hurley (19).

The beneficial effects of both quadriceps-strengthening and aerobic exercise for patients with knee OA, noted in the original recommendations, were confirmed in the Fitness Arthritis and Seniors Trial (20), in which patients with mild disability due to symptomatic knee OA were randomly assigned to aerobic exercise, resistive (muscle-strengthening) exercise, or an education/attention control group. Patients in both exercise groups had modest but significant improvement compared with the control group; this improvement was sustained over an 18-month followup period. In post hoc analyses, the authors found that the degree of adherence to the exercise regimen was significantly associated with the magnitude of improvement in pain and functional limitation. The ability of elderly subjects to maintain conditioning levels of exercise is noteworthy, since many patients with advanced hip or knee OA are sedentary, deconditioned, and at increased risk for cardiovascular disease (21).

Another recent study demonstrated the efficacy of an exercise program in improving muscle strength, mobility, and coordination in patients with OA of either the knee or hip (22). In this study, patients randomly assigned to the exercise group not only had improvement in pain and observed disability, but also reported taking less acetaminophen and had made fewer physician visits by 12 weeks after entry. The effectiveness of exercise was similar in patients with hip or knee OA. These exercise programs, however, require a commitment of time and effort on the part of the patient.

In addition to quadriceps weakness, sensory dysfunction, reflected by a decrease in proprioception, has been documented in patients with knee OA (23,24). Hurley and Scott (25) showed that an easily performed exercise regimen improved knee joint position sense as well as quadriceps strength and performance of ADLs,

and that these improvements were maintained for as long as 6 months.

The 1995 ACR guidelines also recommended that overweight patients with hip or knee OA lose weight. A randomized open trial of an appetite suppressant and low-calorie diet was completed in 40 overweight patients with knee OA; all patients received instruction in an exercise walking program (26). Patients randomly assigned to the appetite suppressant group lost a mean of 3.9 kg over the course of 6 weeks, and also had significant improvement in their knee OA, as measured by the Lequesne algofunctional index. Although this study had limitations, it provided the only data from a randomized trial demonstrating a relationship between loss of body fat (rather than loss of body weight) and improvement in symptoms of knee OA.

As noted in the 1995 ACR recommendations (5,6), proper use of a cane (in the hand contralateral to the affected knee) reduces loading forces on the joint and is associated with a decrease in pain and improvement of function. In addition, patients may benefit from wedged insoles to correct abnormal biomechanics due to varus deformity of the knee (27,28). Another useful maneuver for patients with OA of the knee who have symptomatic patellofemoral compartment involvement is medial taping of the patella (29).

Pharmacologic therapy

All of the pharmacologic agents discussed in this section should be considered additions to nonpharmacologic measures, such as those described above, which are the cornerstone of OA management and should be maintained throughout the treatment period. Drug therapy for pain management is most effective when combined with nonpharmacologic strategies (30).

For many patients with OA, the relief of mild-to-moderate joint pain afforded by the simple analgesic, acetaminophen, is comparable with that achievable with an NSAID (8,10,31-33). Furthermore, Bradley and colleagues failed to demonstrate differences in responses to acetaminophen and ibuprofen in knee OA patients with clinical features of joint inflammation (34). However, this finding was based on a post hoc analysis with limited statistical power that used a definition of inflammation which included joint-line and soft-tissue tenderness or soft-tissue swelling. Eccles and colleagues, in a meta-analysis of trials comparing simple analgesics with NSAIDs in patients with knee OA, did note that NSAID-treated patients had significantly greater improvement in both pain at rest and pain on motion (33).

Two recent trials, findings of which were presented at the ACR's 1999 annual meeting, also provide data on the relative efficacy of acetaminophen and NSAIDs in patients with OA. In one study, acetaminophen and ibuprofen were comparably effective in patients with mild-to-moderate pain, but ibuprofen was statistically superior to acetaminophen in patients with severe pain (35); in the other study, diclofenac was statistically superior to acetaminophen for both pain and function measured with several validated outcome measures (36). Furthermore, two recent studies of patients with OA demonstrated greater preference for NSAIDs than for acetaminophen, although many patients continue to take acetaminophen (13,14). Nevertheless, although a number of patients may fail to obtain adequate relief even with full doses of acetaminophen, this drug merits a trial as initial therapy, based on its overall cost, efficacy, and toxicity profile (33,37). In patients with knee OA with moderate-to-severe pain, and in whom signs of joint inflammation are present, joint aspiration accompanied by intraarticular injection of glucocorticoids or prescription of an NSAID merits consideration as an alternate initial therapeutic approach.

The daily dose of acetaminophen should not exceed 4 gm. Although it is one of the safest analgesics, acetaminophen can be associated with clinically important adverse events. Recent reports have highlighted long-recognized conditions in which increased awareness of potential toxicity is important. For example, because acetaminophen can prolong the half-life of warfarin sodium, careful monitoring of the prothrombin time is recommended in patients taking warfarin sodium who subsequently begin high-dose acetaminophen treatment (38,39). Hepatic toxicity with acetaminophen is rare with doses of ≤ 4 gm/day. Nonetheless, the drug should be used cautiously in patients with existing liver disease and avoided in patients with chronic alcohol abuse because of known increased risk in these settings (40–42). Even though acetaminophen was reported to be weakly associated with end-stage renal disease, the Scientific Advisory Committee of the National Kidney Foundation recommends it as the drug of choice for analgesia in patients with impaired renal function (43).

For those patients who fail to obtain adequate symptomatic relief with the above measures, alternative or additional pharmacologic agents should be considered. The choice should be made after evaluation of risk factors for serious upper gastrointestinal (GI) and renal toxicity. Data from epidemiologic studies show that among persons of age ≥ 65 years, 20–30% of all hospitalizations and deaths due to peptic ulcer disease were

Table 2. Risk factors for upper gastrointestinal adverse events

Age ≥ 65
Comorbid medical conditions
Oral glucocorticoids
History of peptic ulcer disease
History of upper gastrointestinal bleeding
Anticoagulants

attributable to therapy with NSAIDs (44–46). Furthermore, in the elderly, the risk of a catastrophic GI event in patients taking NSAIDs is dose dependent (44). Risk factors for upper GI bleeding in patients treated with NSAIDs include age ≥ 65 years, history of peptic ulcer disease or of upper GI bleeding, concomitant use of oral glucocorticoids or anticoagulants, presence of comorbid conditions, and, possibly, smoking and alcohol consumption (Table 2) (47–49). Risk factors for reversible renal failure in patients with intrinsic renal disease (usually defined as a serum creatinine concentration of ≥ 2.0 mg/dl) who are treated with NSAIDs include age ≥ 65 years, hypertension and/or congestive heart failure, and concomitant use of diuretics and angiotensin-converting enzyme inhibitors (50).

Additional considerations involved in a practitioner's decision to treat the individual OA patient include existing comorbidities and concomitant therapy, as well as the side effects and costs of specific treatments. In individuals with OA of the knee who have mild-to-moderate pain, do not respond to acetaminophen, and do not wish to take systemic therapy, the use of topical analgesics (e.g., methylsalicylate or capsaicin cream) is appropriate as either adjunctive treatment or monotherapy. Capsaicin cream should be applied to the symptomatic joint 4 times daily; a local burning sensation is common, but rarely leads to discontinuation of therapy. A systematic review of topical NSAIDs also demonstrated efficacy in patients with OA (51); there are no published findings of trials comparing the same NSAID administered orally versus topically.

Initiation of treatment in the patient at increased risk for an upper GI adverse event

The options for medical management of OA that has not responded to the above measures in patients who are at increased risk for a serious upper GI adverse event, such as bleeding, perforation, or obstruction, are summarized in Table 3; these include either oral agents or local intraarticular therapy. Two cyclooxygenase 2 (COX-2)-specific inhibitors, celecoxib and rofecoxib, have been studied in patients with OA (52,53). Cele-

Table 3. Pharmacologic therapy for patients with osteoarthritis*

Oral
Acetaminophen
COX-2-specific inhibitor
Nonselective NSAID plus misoprostol or a proton pump inhibitor†
Nonacetylated salicylate
Other pure analgesics
Tramadol
Opioids
Intraarticular
Glucocorticoids
Hyaluronan
Topical
Capsaicin
Methylsalicylate

* The choice of agent(s) should be individualized for each patient as noted in the text. COX-2 = cyclooxygenase 2; NSAID = nonsteroidal antiinflammatory drug.

† Misoprostol and proton pump inhibitors are recommended in patients who are at increased risk for upper gastrointestinal adverse events.

coxib has been found to be more effective than placebo and comparable in efficacy with naproxen in patients with hip or knee OA (54–56). Rofecoxib has also been found to be more effective than placebo and is comparable in efficacy with both ibuprofen and diclofenac in patients with hip or knee OA (57,58). Endoscopic studies have shown that celecoxib and rofecoxib are both associated with an incidence of gastroduodenal ulcers lower than that of the comparator NSAIDs and similar to that of placebo (52,59–61). These data suggest an advantageous safety profile compared with that of nonselective NSAIDs, especially for treatment of high-risk patients. However, the results of large, long-term studies that were designed to demonstrate differences between COX-2-specific inhibitors and nonselective NSAIDs with respect to major GI clinical outcomes have not yet been published. Such studies have been completed, and results are expected to be published some time in 2000.

Of further advantage with respect to upper GI bleeding, neither of the COX-2-specific inhibitors has a clinically significant effect on platelet aggregation or bleeding time. This is a consideration, especially in pre- and perioperative management of patients with OA (in whom nonselective NSAIDs have traditionally been discontinued as long as 2 weeks prior to surgery), as well as for patients taking warfarin sodium. Accordingly, these agents appear preferable to currently available nonselective NSAIDs for use in patients at risk for upper GI complications. Additionally, at doses recommended for treatment of OA, both celecoxib and rofecoxib appear to be better tolerated, with a lower incidence of

dyspepsia and other GI side effects, than comparator nonselective NSAIDs (59,62). Like nonselective NSAIDs, however, COX-2-specific inhibitors can cause renal toxicity. Caution must be exercised, therefore, if they are used in patients with hypertension, congestive heart failure, or mild-to-moderate renal insufficiency; they should not be used in patients with severe renal insufficiency. In addition, the use of celecoxib is contraindicated in patients with a history of an allergic reaction to a sulfonamide.

An alternative to the use of COX-2-specific inhibitors is the use of nonselective NSAIDs with gastroprotective agents, as described in the 1995 ACR recommendations (5,6) and endorsed by the American College of Gastroenterology (49). As noted above, serious adverse upper GI events attributed to NSAIDs in the elderly are dose dependent. Therefore, if nonselective NSAIDs are used, they should be started in low, analgesic doses and increased to full antiinflammatory doses only if lower doses do not provide adequate symptomatic relief. In the patient who is at increased risk for a serious upper GI adverse event, gastroprotective agents should be used even if nonselective NSAIDs are given at low dosage.

In a study of 8,843 patients with RA, 200 μ g misoprostol 4 times a day reduced the incidence of complicated ulcers, including those with perforation, bleeding, and obstruction, by 51% (63). In a 12-week, randomized, double-blind, placebo-controlled endoscopy study, 200 μ g misoprostol 3 times a day had comparable efficacy in preventing both gastric and duodenal ulcers; however, 200 μ g misoprostol twice a day conferred significantly less protection from gastric ulcers (64). Nonetheless, side effects, particularly diarrhea and flatulence, may occur with this agent, in a dose-dependent manner (64). Alternative approaches to prophylaxis with misoprostol include the use of high-dose famotidine or omeprazole, both of which have been shown to be effective in treating and preventing NSAID gastropathy in carefully conducted endoscopy studies (65–68). H_2 blockers in usual doses, however, have not been found to be as effective as misoprostol (67). Either 20 mg/day or 40 mg/day omeprazole was as effective as 200 μ g misoprostol twice a day in the treatment of existing ulcers, and was better tolerated and associated with a lower rate of relapse (68). Proton pump inhibitors, however, have not been approved by the FDA for use in prophylaxis, although they are being widely used for that purpose.

In addition to their effects on the GI mucosa, nonselective NSAIDs inhibit platelet aggregation, fur-

ther increasing the risk of GI bleeding. Nonacetylated salicylates (e.g., choline magnesium trisalicylate, sal-salate) are not accompanied by the antiplatelet effects or renal toxicity associated with nonselective NSAIDs (69), and can also be considered in management of the high-risk patient; however, ototoxicity and central nervous system toxicity at clinically efficacious doses may limit their use.

An alternative approach to the use of oral agents in the palliation of joint pain is the use of intraarticular therapy such as hyaluronan (hyaluronic acid) or glucocorticoids. Two preparations of intraarticular hyaluronan have been approved by the FDA for the treatment of knee OA patients who have not responded to a program of nonpharmacologic therapy and acetaminophen. To date, differences in clinical efficacy between these preparations as a function of molecular weight have not been demonstrated (70). Because the duration of benefit reported for these agents exceeds their synovial half-life, their mechanisms of action are unclear; proposed mechanisms include inhibition of inflammatory mediators such as cytokines and prostaglandins, stimulation of cartilage matrix synthesis and inhibition of cartilage degradation, and a direct protective action on nociceptive nerve endings.

In clinical trials of intraarticular hyaluronan preparations, pain relief among those who completed the study was significantly greater than that seen after intraarticular injection of placebo, and comparable with that seen with oral NSAIDs (71–73). In addition, pain relief among those who completed the study was comparable with or greater than that with intraarticular glucocorticoids (73). Although pain relief is achieved more slowly with hyaluronan injections than with intraarticular glucocorticoid injections, the effect may last considerably longer with hyaluronan injections (73). Intraarticular hyaluronan therapy is indicated for use in patients who have not responded to a program of nonpharmacologic therapy and simple analgesics; intraarticular hyaluronan injections may be especially advantageous in patients in whom nonselective NSAIDs and COX-2-specific inhibitors are contraindicated, or in whom they have been associated either with a lack of efficacy or with adverse events. Limited data are available concerning the effectiveness of multiple courses of intraarticular hyaluronan therapy (74). Transient mild-to-moderate pain at the injection site may occur; occasionally, mild-to-marked increases in joint pain and swelling have been noted following hyaluronan injection.

Intraarticular glucocorticoid injections are of value in the treatment of acute knee pain in patients with

OA, and may be particularly beneficial in patients who have signs of local inflammation with a joint effusion. When joints are painful and swollen, aspiration of fluid followed by intraarticular injection of a glucocorticoid preparation (e.g., up to 40 mg triamcinolone hexacetonide) is an effective short-term method of decreasing pain and increasing quadriceps strength (73,75). Injection can be used as monotherapy in selected patients or as an adjunct to systemic therapy with an analgesic, a nonselective NSAID, or a COX-2-specific inhibitor. Joints should be aspirated/injected using aseptic technique, and the fluid should be sent for a cell count. Gram stain and culture should be performed if infection is suspected. Some patients may experience a mild flare of synovitis due to a reaction to the crystalline steroid suspensions; however, these postinjection flares are temporary and can be treated with analgesics and cold compresses. The risk of introducing infection into an OA joint is exceedingly low if standard aseptic technique is used.

Tramadol, a centrally acting oral analgesic, is a synthetic opioid agonist that also inhibits reuptake of norepinephrine and serotonin. It has been approved by the FDA for the treatment of moderate-to-severe pain and can be considered for use in patients who have contraindications to COX-2-specific inhibitors and nonselective NSAIDs, including impaired renal function, or in patients who have not responded to previous oral therapy. Although there are numerous studies of the use of tramadol in general pain, few controlled studies have examined its use in OA. The efficacy of tramadol has been found to be comparable with that of ibuprofen in patients with hip and knee OA (76), and it has been found to be useful as adjunctive therapy in patients with OA whose symptoms are inadequately controlled with NSAIDs (77). Mean effective daily doses of tramadol have generally been in the range of 200–300 mg, given in 4 divided doses. Side effects are common and include nausea, constipation, and drowsiness. Despite its opioid pharmacology, a comprehensive surveillance program has failed to demonstrate significant abuse, and tramadol remains an unscheduled agent.

Patients who do not respond to or cannot tolerate tramadol and who continue to have severe pain may be considered candidates for more potent opioid therapy (30). In one study, the combination of codeine plus acetaminophen was shown to provide significantly better analgesia than acetaminophen alone in patients with hip OA, although one-third of patients receiving the combination discontinued therapy due to nausea, vomiting, dizziness, or constipation (78). In a short-term study of

acute pain in patients with hip or knee OA, no difference in analgesic efficacy was demonstrated between combinations of acetaminophen with either dextropropoxyphene or codeine; however, the combination with dextropropoxyphene was significantly better tolerated (79). The American Pain Society and American Academy of Pain Medicine recently published joint guidelines on the use of more potent opioids in the management of chronic, nonmalignant pain (80). Tolerance, dependence, and adverse effects, including respiratory depression and constipation, may occur with opioid usage.

Although the efficacy of therapy with combinations of the above pharmacologic agents has not been established in controlled clinical trials, in general, it is reasonable to use the recommended agents in combination in an individual patient. However, only a single NSAID should be used at any given time, the sole exception being the concomitant use of a cardioprotective dose of aspirin (81–325 mg/day) with other NSAIDs. Even these low doses of aspirin, however, will increase the risk of upper GI bleeding in patients taking NSAIDs. In this regard, it should be noted that the incidence of endoscopically identified ulcers in patients taking a COX-2-specific inhibitor and a cardioprotective dose of aspirin was lower than that in comparator groups taking nonselective NSAIDs with or without concomitant low-dose aspirin (52).

Initiation of treatment in the patient who is not at increased risk for an upper GI adverse event

The approach recommended for treatment of patients not at increased risk for an upper GI adverse event is similar to that described above (Table 3). As in the case of patients at increased risk for a serious upper GI adverse event, if a nonselective NSAID is used, it should be started at a low, analgesic dosage which should be increased only if it is ineffective in providing symptomatic relief. Use of concomitant gastroprotective therapy with misoprostol or a proton pump inhibitor, however, is not recommended in the low-risk patient.

Management of OA in the patient who is already taking an NSAID

The above sections address the management of OA in patients who have not had prior treatment of their disease. In OA patients who are already taking an NSAID, but who have not incorporated relevant non-pharmacologic measures (e.g., an exercise program, weight loss program, adherence to principles of joint

protection) into their treatment program, such measures should be implemented. This may permit reduction of the dosage of NSAID or replacement of the NSAID with acetaminophen. In all patients whose symptoms are well controlled, attempts should be made periodically to reduce the dosage of NSAID and/or analgesic agents and to determine whether it is possible to use such agents on an as-needed basis, rather than in a fixed dosing regimen.

Tidal irrigation

While the 1995 ACR guidelines recommended that tidal irrigation (TI) should be considered for those patients with knee OA that did not respond satisfactorily to nonpharmacologic and pharmacologic measures (6), it was cautioned that information did not exist concerning the magnitude of the placebo response to this procedure. An ongoing, sham-controlled study of TI is currently in progress, but results are not available. The placebo response to an invasive procedure, such as TI, may be large, and results of properly controlled studies of TI, which would permit guidance in this area, are not yet available. Accordingly, although some data suggest that TI may be efficacious in some patients (6,81), the subcommittee believes that a statement concerning the role for this modality should await further study.

Treatment of the patient with hip OA

It should be noted that therapy for OA of the hip is similar to treatment of OA of the knee, except for a few minor differences. Intraarticular hyaluronan therapy is not approved for hip OA, and there are no published studies regarding its efficacy in patients with hip OA. Topical agents have not been studied in hip OA, and their efficacy is questionable because of the depth of that joint. Intraarticular glucocorticoid injections have not been studied in patients with hip OA, but are used occasionally and may be efficacious. Injections performed without fluoroscopic guidance should be administered only by those experienced in this approach. Modalities of physical therapy for patients with hip OA differ from those used in patients with OA of the knee. Consultation with a physical therapist should be considered as part of the overall management.

Surgical treatment

Patients with severe symptomatic OA who have pain that has failed to respond to medical therapy and

who have progressive limitation in ADLs should be referred to an orthopedic surgeon for evaluation. No well-controlled trials of arthroscopic debridement with or without arthroplasty have been conducted, and the utility of this intervention for the treatment of knee OA is unproven. In appropriately selected patients who are not yet candidates for total joint arthroplasty, osteotomy may provide pain relief and prevent progression of disease. Total joint arthroplasty provides marked pain relief and functional improvement in the vast majority of patients with OA (82,83), and has been shown to be cost effective in selected patients (83,84). Indications for total hip replacement, developed at a National Institutes of Health (NIH) Consensus Conference, include "radiographic evidence of joint damage and moderate to severe persistent pain or disability, or both, that is not substantially relieved by an extended course of nonsurgical management" (85). While there are no published evidence-based indications for total knee replacement, Dieppe and colleagues have summarized the indications derived from 3 consensus groups of orthopedic surgeons (83). Outcomes depend upon the timing of the surgery, the experience of the surgeon and the hospital with the procedure, and the patient's preoperative medical status, peri- and postoperative management, and rehabilitation.

Agents under investigation

While a number of studies support the efficacy of both glucosamine and chondroitin sulfate for palliation of joint pain in patients with knee OA (86,87), the subcommittee believes that it is premature to make specific recommendations about their use at this time because of methodologic considerations, including lack of standardized case definitions and standardized outcome assessments, as well as insufficient information about study design in a number of these published reports. A pivotal clinical trial being planned by the NIH should help define the role of these agents, singly and in combination, in the treatment of patients with knee OA.

In addition, currently existing data are insufficient or inadequate to permit the subcommittee to make definitive recommendations about the use of devices, such as pulsed electromagnetic fields and lasers. Further research is needed on vitamin deficiencies, which have been suggested as possible causes of (or aggravating factors in) OA, before dietary supplementation can be recommended for prevention or treatment of this disease (88). Similarly, the value, if any, of other nutritional supplements, including supraphysiologic doses of anti-

oxidant vitamins, remains to be determined. In addition, therapeutic approaches such as acupuncture are difficult to evaluate and recommend because of large placebo effects of invasive procedures and the lack of adequate sham-controlled studies. An ongoing, pivotal, randomized, sham-controlled trial of acupuncture, supported by the NIH, is under way; this trial should help define acupuncture's role in the treatment of patients with knee OA.

The 1995 ACR recommendations briefly mentioned preliminary studies of disease-modifying OA drugs (DMOADs), drugs whose action is not aimed principally at the control of symptoms, but instead at the prevention of structural damage in normal joints at risk for development of OA, or at the progression of structural damage in joints already affected by OA. For the most part, such approaches have been aimed at inhibiting the breakdown of articular cartilage by matrix metalloproteinases, or at stimulating repair activity by chondrocytes. Although a number of agents are under study, including matrix metalloproteinase inhibitors and growth factors, no agent has been shown to have a DMOAD effect in humans, and none are available for this indication.

In addition to therapeutic agents targeted toward prevention, retardation, or reversal of cartilage breakdown in OA, significant advances, such as autologous chondrocyte transplantation (89), cartilage repair using mesenchymal stem cells (90), and autologous osteochondral plugs (mosaicplasty) (91), are being investigated for repair of focal chondral defects. These procedures are not currently indicated in the treatment of patients with OA.

Given the advances in therapy which can be anticipated for patients with OA, the subcommittee expects that current recommendations will change as new knowledge of the disease unfolds and new therapies become available.

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